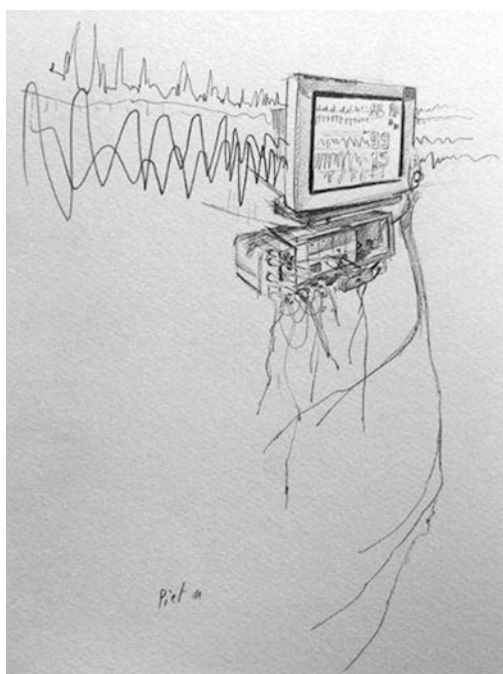


Wave Intensity Analysis: Sex-Specific Differences in Hemodynamic and Ventilatory Responses to Graded Exercise—Echocardiographic Measurements

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Midori Tanaka, Motoaki Sugawara, Yasuo Ogasawara, and Kiyomi Niki



Wave intensity analysis. Artwork by Piet Michiels, Leuven, Belgium

M. Tanaka (✉) · M. Sugawara
Faculty of Health Care Sciences, Himeji Dokkyo
University, Himeji, Japan
e-mail: mikko17@gm.himeji-du.ac.jp

Y. Ogasawara
Department of Medical Engineering, Kawasaki University
of Medical Welfare, Okayama, Japan

K. Niki
Department of Medical Engineering, Tokyo City
University, Tokyo, Japan

Abstract

Background: The differences in hemodynamic and ventilatory responses to graded exercise between men and women have not been well documented. Using wave intensity (WI) analysis, which is useful for analyzing ventriculo-arterial interaction, we aimed to elucidate the sex-specific differences.

Methods: We enrolled 48 healthy subjects (24 men and 24 women, age 21.3 ± 1.6 and 20.5 ± 0.9 years, n.s. [not significant]). Using ultrasonic diagnostic equipment, we measured WI, arterial stiffness parameter (β), force-frequency relation (FFR) and other hemodynamic parameters in the carotid artery before and during graded bicycle exercise. We also analyzed expired gas volume (VE) during the exercise. The workload was increased stepwise by 20 W at 1-min intervals up to respiratory compensation (RC) point through the anaerobic threshold (AT). WI is defined as $WI = (dP/dt) (dU/dt)$, where P is blood pressure, U is velocity, and t is time. The peak value of WI (W_1) increases with left ventricular (LV) peak dP/dt, in other words, an index of cardiac contractility. The FFR was obtained as the linear regression line of W_1 on heart rate. β is defined as $\beta = \ln (P_s/P_d) / [(D_s - D_d)/D_d]$, where D is the arterial diameter, and suffixes s and d indicate systolic and diastolic, respectively.

Results: There was no difference in the body mass index between men and women. Carbon dioxide outputs (VCO_2) did not differ at rest, but those at AT and RC were greater in men. Oxygen consumptions (VO_2) in men and women at rest did not differ, but those in men at AT and RC were greater. Workloads per body weight in men and women did not differ at AT, but they were greater in men at RC. Systolic pressures at rest, AT and RC were greater in men than women. Heart rates in men and women did not differ at any stage of the graded exercise. W_1 did not differ at rest and AT, but it was greater in men than women at RC. The slope of the FFR during the period from rest to AT did not differ between men and women. However, the slope of the FFR during the period from AT to RC was greater in men.

Conclusions: The reached values of workload/weight at RC, VCO_2 at AT and RC, VO_2 at AT and RC, W_1 at RC, and the slope of the

FFR during the period from AT to RC were greater in men than women.

Keywords

Graded exercise · Ultrasonic measurements · Cardiopulmonary test · Wave intensity · Force-frequency relation

Introduction

The differences in hemodynamic and ventilatory responses to graded exercise between men and women have not been well documented. In normal subjects, cardiac contractility increases with an increase in heart rate (HR). This phenomenon is called the “force-frequency relation” (FFR) [1–3]. However, increased HR does not necessarily increase cardiac contractility in patients with heart disease [4, 5]. Conventionally, FFRs were obtained by measuring the maximum rate of left ventricular (LV) pressure increase (peak dP/dt) with a catheter-tipped micromanometer as an index of cardiac contractility and using atrial pacing to change HR (Peak dP/dt – HR relation). This conventional method is an invasive method and cannot be used repeatedly in the clinical setting.

Wave intensity (WI) is a hemodynamic parameter defined as the product of the time-derivatives of pressure and velocity [6, 7]. Using ultrasonic equipment, WI is obtained non-invasively. It has been demonstrated that the magnitude of the first peak of WI increases with an increase in LV peak dP/dt [7]. During exercise, HR increases with an increase in workload; therefore, atrial pacing is not needed for changing HR. Moreover, force-frequency effects on the inotropic state of the intact left ventricle are markedly enhanced by exercise [8]. By measuring WI during graded exercise, we can obtain the FFR non-invasively [9].

We measured WI, FFR and other hemodynamic parameters and ventilatory parameters to investigate sex-specific differences in the

responses of these parameters to the graded exercise among healthy young subjects.

Methods

Subjects

We enrolled 24 healthy men and 24 age-matched healthy women (age 21.3 ± 1.6 vs. 20.5 ± 0.9 years, $P = 0.11$). All subjects provided informed consent, and the Ethics Committee of Himeji Dokkyo University approved the study protocol.

Using ultrasonic diagnostic equipment, we measured wave intensity (WI), arterial stiffness parameter (β), force-frequency relation (FFR) and other hemodynamic parameters in the carotid artery before and during graded bicycle exercise.

We also recorded cardiopulmonary data with a breath-by-breath cardiopulmonary testing system (AE300S, MINATO Co LTD, Japan).

Theoretical Consideration of Wave Intensity

Parker et al. [10] proposed a novel index related to wave transmission and named it “wave intensity.” They derived the features of WI using a mathematically sophisticated method called “the method of characteristics.” However, the same features and further physiological meanings can be obtained by elementary methods in the following way.

Let P_f and P_b be the forward and the backward component of pressure waveform and U_f and U_b be those of velocity waveform, respectively. Then we have

$$P = P_0 + P_f + P_b, \quad (11.1)$$

$$U = U_f + U_b, \quad (11.2)$$

where P and U are measured instantaneous pressure and velocity, and P_0 is the end-diastolic pressure in the artery. On condition that the pulse-wave velocity (PWV) in the artery, c , is

available and is constant during each cardiac cycle (partly linear approximation), we have

$$P_f = \rho c U_f, \quad (11.3)$$

$$P_b = -\rho c U_b, \quad (11.4)$$

where ρ is the blood density. Eqs. (11.3) and (11.4) are often referred to as the “water hammer formula.” From Eqs. (11.1) and (11.2), we obtain

$$P_f = P - P_0 - P_b, \quad (11.5)$$

$$U_f = U - U_b. \quad (11.6)$$

Substituting Eq. (11.4) in Eq. (11.5) and using Eqs. (11.3) and (11.6), we have

$$P_f = P - P_0 + \rho c U_b, \quad (11.7)$$

$$P_f = \rho c U_f = \rho c U - \rho c U_b. \quad (11.8)$$

Adding Eq. (11.7) and Eq. (11.8) and dividing the result by 2, we obtain

$$P_f = (P - P_0 + \rho c U)/2. \quad (11.9)$$

Similarly, we obtain

$$P_b = (P - P_0 - \rho c U)/2. \quad (11.10)$$

WI is defined as

$$WI = (dP/dt)(dU/dt). \quad (11.11)$$

Substituting Eqs. (11.1) and (11.2) in Eq. (11.11), and bearing in mind that P_0 is constant, we have

$$\begin{aligned} WI &= (dP_f/dt + dP_b/dt)(dU_f/dt + dU_b/dt) \\ &= (dP_f/dt)(dU_f/dt) + (dP_b/dt)(dU_f/dt) \\ &\quad + (dP_f/dt)(dU_b/dt) + (dP_b/dt)(dU_b/dt) \end{aligned}$$

Because

$$(dP_b/dt)(dU_f/dt) = -\rho c (dU_b/dt)(dU_f/dt)$$

$$\text{and } (dP_f/dt)(dU_b/dt) = \rho c (dU_f/dt)(dU_b/dt),$$

we have

$$\begin{aligned} WI &= (dP_f/dt)(dU_f/dt) + (dP_b/dt)(dU_b/dt) \\ &= (dP_f/dt)^2/\rho c - (dP_b/dt)^2/\rho c \end{aligned} \quad (11.12)$$

Here,

$$WI_f = (dP_f/dt)(dU_f/dt) = (dP_f/dt)^2/\rho c$$

$$\text{and } WI_b = (dP_b/dt)(dU_b/dt) = -(dP_b/dt)^2/\rho c$$

are the forward and backward components of WI, respectively.

The physiologically important feature that follows from the previous relationship is that forward components are shown always to contribute positively to WI $[(dP_f/dt)^2/\rho c]$, whereas backward components always contribute negatively $[-(dP_b/dt)^2/\rho c]$. This is true whether dP_f/dt or dP_b/dt is positive or negative. Thus, we reach the assertion that a positive value of WI indicates that forward-traveling waves predominate, whereas a negative value indicates that backward-traveling waves predominate.

WI has another important feature. During the period of the first positive peak, which appears in early ejection (Fig. 11.1), P_b and U_b are practically zero, and hence WI_b is also practically zero. Thus, we have

$$\begin{aligned} WI &= WI_f = (dP_f/dt)^2/\rho c \\ &= (dP/dt)^2/\rho c, \end{aligned} \quad (11.13)$$

where P is actually measured pressure. Let W_1 be the height of the first peak (Fig. 11.1); then we have

$$W_1 = (\text{Peak } dP/dt)^2/\rho c.$$

When peak dP/dt is measured in the ascending aorta, aortic peak dP/dt is approximately equal to LV peak dP/dt unless there is aortic stenosis. The strong correlation between W_1 in the aorta and LV peak dP/dt ($r = 0.84$, $P < 0.0001$) was confirmed by animal experiments [11].

Noninvasive Measurements of Wave Intensity

In our method of obtaining carotid arterial WI [12], the carotid diameter-change waveform was used as a surrogate for the carotid-pressure

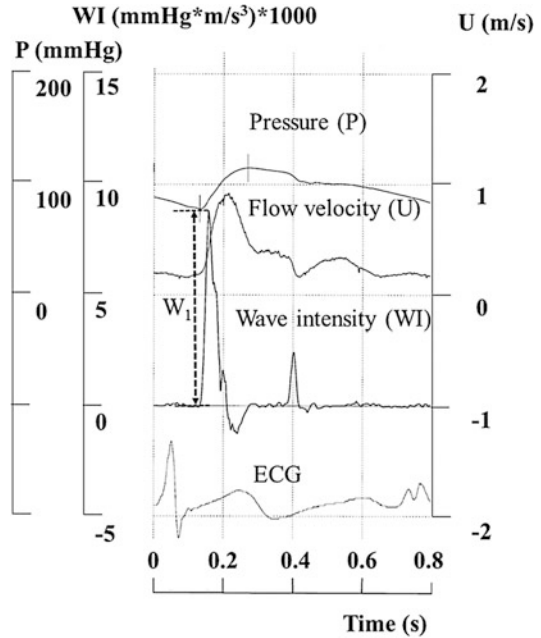


Fig. 11.1 Representative recordings of carotid arterial pressure-change waveform (P), blood flow-velocity waveform (U), calculated WI, and ECG in a healthy human. WI is defined as $WI = (dP/dt)(dU/dt)$

waveform. The blood-flow velocity averaged along the Doppler beam (Fig. 11.2, line B) crossing the carotid artery was measured using range-gated color-Doppler signals. Because the carotid artery is apart from the ascending aorta, carotid arterial W_1 may not represent LV peak dP/dt . Nevertheless, the correlation between carotid arterial W_1 and LV peak dP/dt was confirmed by clinical measurements (Fig. 11.3) [13]. The FFR was obtained as the linear regression line of W_1 on HR. Then we analyzed the differences in the slope of W_1 -HR relations.

We also measured stiffness parameter (β) in the carotid artery. The definition of the stiffness parameter β is

$$\beta = \ln(P_s/P_d)/[(D_s - D_d)/D_d], \quad (11.14)$$

where D is the arterial diameter, and suffixes s and d indicate systolic and diastolic, respectively. β is considered to be independent of pressure [14].

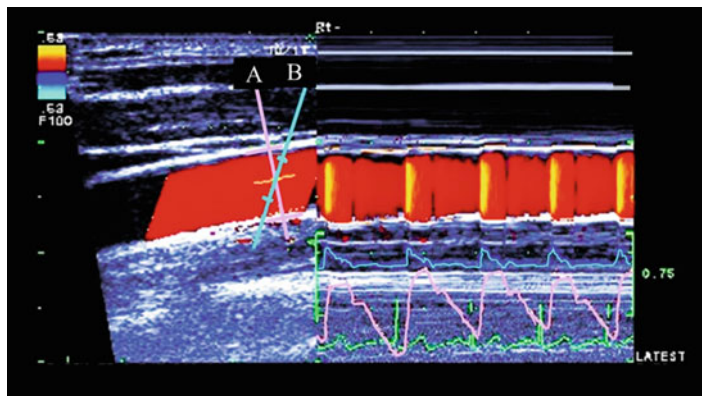
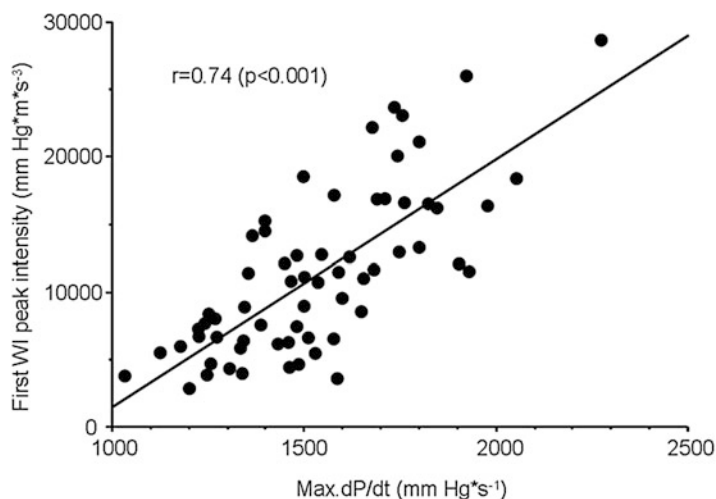


Fig. 11.2 Measurements of pressure-change waveform and blood velocity. Left: Long-axis view of the common carotid artery and ultrasound beams. By setting the tracking positions, displayed as small pink bars on the echo-tracking beam (line A), to arterial walls, echo tracking automatically starts. The blood flow-velocity averaged along the Doppler beam (line B) crossing the artery was measured using range-gated color-Doppler signals. Right:

The diameter-change waveform is calculated by subtracting the distance to the near wall from that to the far wall. The maximum and minimum values of the diameter-change waveform are calibrated by P_s and P_d . The pressure-change waveform is displayed on the M-mode view. The blood flow-velocity waveform is also displayed on the M-mode view

Fig. 11.3 Relationship between the magnitude of the first peak (W_1) of carotid arterial WI obtained by ultrasonic methods and the maximum rate of LV-pressure increase (max dP/dt) (from Ohte N et al. [13] with investigators' permission)



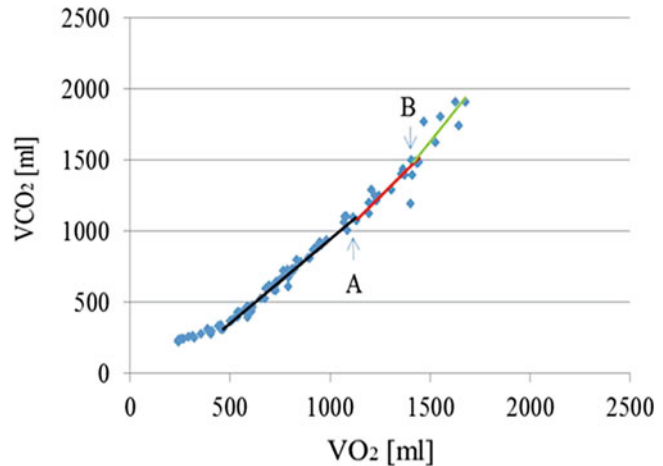
Determination of Anaerobic Threshold and Respiratory Compensation Points

The AT was determined as the point of deflection of VCO_2 versus the VO_2 plot obtained by computerized regression analysis (V-slope method) (Fig. 11.4). The RC was determined by the following: (1) the point of deflection of VE versus VCO_2 ; (2) the minimal value or nonlinear increase of VE/VCO_2 ; and (3) the point at which end-tidal CO_2 pressure starts to decrease.

Protocol

First, before the measurements, we had the subjects lie down in semi-supine position for 10 min on the recumbent type ergometer. The location to be measured was the common carotid artery at approximately 2 cm proximal to the carotid bulb. We used scanning in the long-axis view and obtained a B-mode image of a longitudinal section of the artery (Fig. 11.2, left). With the B- and M-mode scans displayed simultaneously on a split screen, the

Fig. 11.4 Representative recordings of the breath-by-breath cardiopulmonary test during the graded exercise. VCO_2 = CO_2 output; VO_2 = O_2 consumption; point A = AT; and point B = RC



echo-tracking system tracked the vessel-wall movements to produce displacement waveforms of the anterior and posterior artery walls (Fig. 11.2, right). This gave the diameter-change waveforms.

Next, after taking the measurements at rest, graded bicycle exercise was performed starting at an initial workload of 20 W and lasting for 2 min; thereafter, the workload was increased stepwise by 20 W at 1-min intervals up to the respiratory compensation point (RC) through the anaerobic threshold (AT). Electrocardiogram was continuously monitored. We measured W_1 and other hemodynamic parameters during the exercise. We also analyzed VE during the exercise.

Data Analysis

The obtained data are expressed as mean \pm SD. The scatter diagram of the points (HR, W_1) for the data during exercise from each subject was analyzed by the linear regression method, and the regression line was considered the FFR. Comparisons between men and women were performed by two-way analysis of variance followed by Bonferroni test when necessary.

Results

There were differences in height and weight between men and women (height 172.5 ± 6.4 vs. 159.5 ± 5.0 cm, $P < 0.0001$;

weight 63.1 ± 11.8 vs. 53.4 ± 7.7 kg, $P < 0.0001$). However, there was no difference in body mass index (BMI) between men and women (BMI 21.1 ± 2.9 vs. 21.0 ± 2.6 kg/m², n.s.). There were no differences in VCO_2 between men and women at rest, but those at AT and RC were greater in men than women (Fig. 11.5, left). VO_2 in men and women at rest did not differ, but VO_2 measurements in men at AT and RC were greater than those in women (Fig. 11.5, right). Workloads/body weight in men and women did not differ at AT, but they were greater in men at RC (Fig. 11.6). Systolic pressures (P_s) at rest, AT and RC were greater in men than in women (Fig. 11.7, left). Diastolic pressure (P_d) at AT was greater in men than women, but there were no differences in P_d at rest and RC (Fig. 11.7, right). HR measurements in men and women did not differ at any stage of the graded exercise (Fig. 11.8). P_s/P_d in men did not differ from that in women throughout the period of the graded exercise (Fig. 11.9, left). $(D_s - D_d)/D_d$ increased in men, but it did not change in women during the exercise (Fig. 11.9, middle). As a result, β in men did not change during the exercise, but β in women significantly increased at AT and RC (Fig. 11.9, right).

At any stage of the graded exercise, carotid arterial blood flow volume during a cardiac cycle (carotid arterial stroke volume) and carotid arterial blood flow volume per minute (carotid arterial output) in men and women did not differ (Fig. 11.10, left and right). W_1 did not differ at

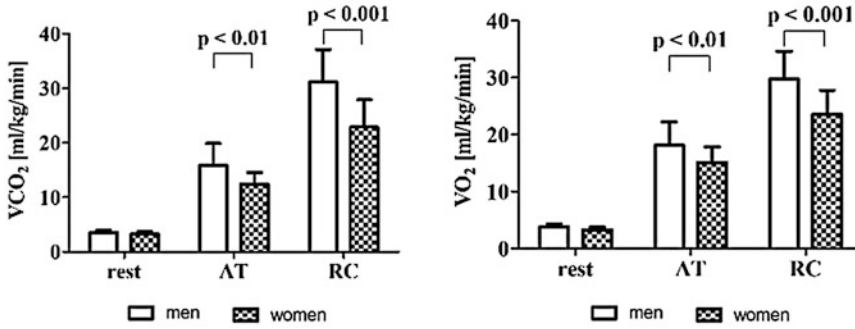


Fig. 11.5 Comparison of CO₂ outputs (VCO₂) (left) and O₂ consumptions (VO₂) (right) at rest, AT and RC point during graduated exercise in men and women

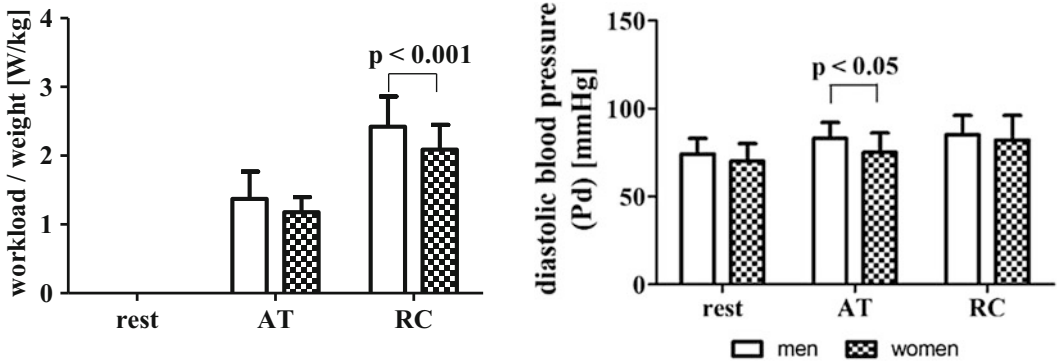


Fig. 11.6 Comparison of W₁ and W_R (workload/body weight) at AT and RC point during graded exercise between men and women

rest and AT, but it was greater in men than in women at RC (Fig. 11.11). In men, FFR slope increased during the period from AT to RC compared with the period from rest to AT (Fig. 11.12, left). However, in women, the slope did not change significantly throughout the period from rest to RC (Fig. 11.12, right). FFR slope during the period from rest to AT did not differ between men and women. However, the slope of the FFR during the period from AT to RC was greater in men than in women (Fig. 11.13).

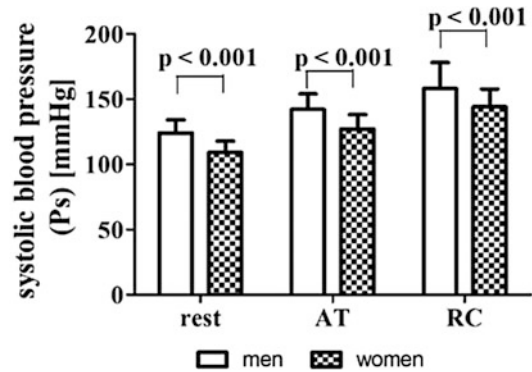


Fig. 11.7 Comparison of Ps and Pd at rest, AT and RC point during graded exercise between men and women

Discussion

There were no significant differences in VCO₂ and VO₂ between the men and women groups at rest. However, men had greater VCO₂ and VO₂ at AT and RC than did women. The workload/body

weight observed at AT in men did not differ significantly from that in women, but men showed greater workload/body weight at RC than that of women. The male and female study groups were age- and BMI-matched, but men had greater heights and weights than women. Because the lung volume and forced vital capacity (FVC)

mainly depend on height, men are considered to have greater lung volumes and FVC measurements. Murias [15] reported that in young women, during ramp incremental exercise, the matching of O₂ delivery to O₂ use within the

exercising limb is less effective compared with that in men, likely reflecting impairments in blood flow. Although the mechanisms responsible for the discrepancies between sexes are currently unclear, these may account for the above-mentioned differences.

Studies using the technique of 24-h ambulatory blood-pressure monitoring have shown that blood pressure is greater in men than in women at similar age [16, 17]. In this study, Ps was greater in men at rest, AT and RC. Diastolic pressure did not differ between men and women at rest and RC, but it differed at AT. Women have been noted to have greater HRs at rest [18]. However, in this study, there were no significant differences in HR at rest, AT and RC between men and women. During the exercise, carotid arterial stroke volume decreased with an increase in HR. There were no differences in carotid arterial stroke volume and carotid arterial output between men and women during the exercise.

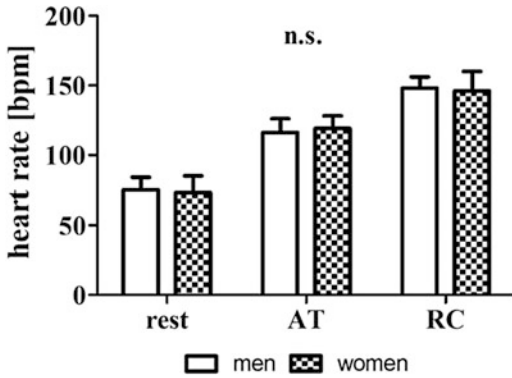


Fig. 11.8 Comparison of HR at rest, AT and RC point during graded exercise between men and women

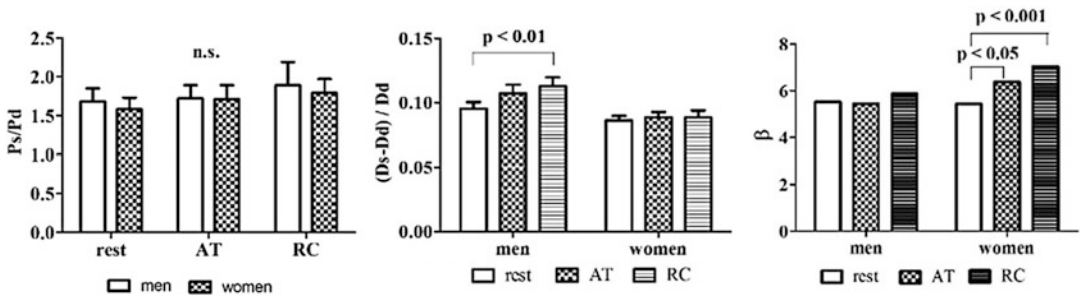


Fig. 11.9 Comparison of Ps/Pd (left), (Ds - Dd)/Dd (middle), and beta (right) at rest, AT and RC point during graded exercise between men and women

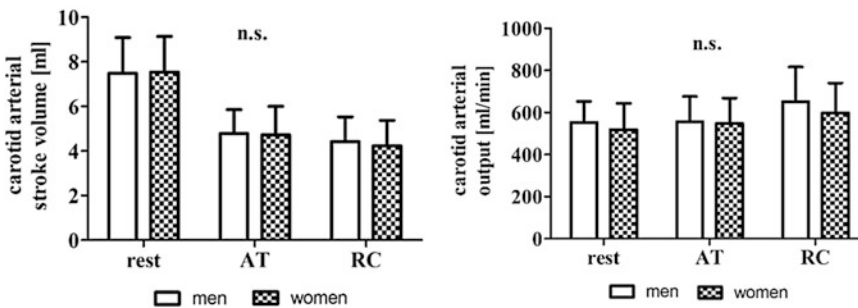


Fig. 11.10 Comparison of carotid arterial stroke volumes and carotid arterial outputs at rest, AT and RC point during graded exercise between men and women

Various theories have been offered to explain the sex-specific differences in change in ejection performance during exercise. Among them, one article recently suggested that central artery stiffness increases during exercise [19], and increased central artery stiffness has a direct impact on myocardial energetics: There is an increased energetic cost to maintain a given ejection/outflow due to a less-compliant central vasculature. This may account, at least in part, for the sex-specific differences in ejection performance during exercise.

Theoretically, the above-mentioned inference is reinforced in the following way. WI analyses assert that during the period of the first positive peak of WI (Fig. 11.1), effects of reflected waves are negligible and the contours of pressure and velocity waves are dominated by forward waves only [7, 10], in other words, $P_b = 0$ and $U_b = 0$. Under such conditions, Eqs. (11.1) and (11.2) give

$$P - P_0 = P_f, \text{ and } U = U_f.$$

Substituting the previous relations in Eq. (11.3), we obtain

$$P - P_0 = \rho c U. \quad (11.15)$$

Let us consider the WI in the ascending aorta. P and U are aortic pressure and velocity at any time during the period of the first positive peak of WI; P_0 is aortic end-diastolic pressure; and ρ and c are the blood density and the PWV, respectively [20]. Although ρc looks like resistance to flow, U , and is sometimes called “characteristic impedance” [21], it has no relation to the viscous systemic resistance. Nevertheless, ρc plays the role of afterload encountered by the left ventricle during initial ejection. Most of the studies evaluated arterial stiffness by measuring PWV. Conventional methods of measuring c have been based on two-point measurements, in other words, measurement of the time of travel of the wave over a known distance. Therefore, c measured over a relatively long distance is the integration of regional c in each artery involved within that range. In contrast, carotid arterial stiffness parameter β was measured at one point. Thus, changes in β may not represent overall changes in arterial stiffness. Nevertheless, the Swiss SAPALDIA cohort study reported a strong correlation ($r = 0.7, P < 0.001$) between brachial–ankle c and the carotid arterial distensibility coefficient, which is approximately the inverse of β [22]. Consequently, we consider that changes in carotid arterial β are associated with changes in c . Thus, the increase in β suppresses the indices of LV-ejection performance.

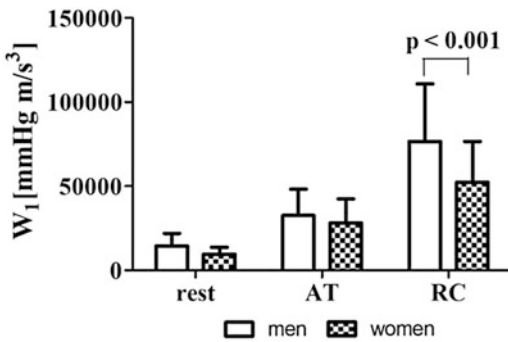


Fig. 11.11 Comparison of W_1 at rest, AT and RC point during graded exercise between men and women

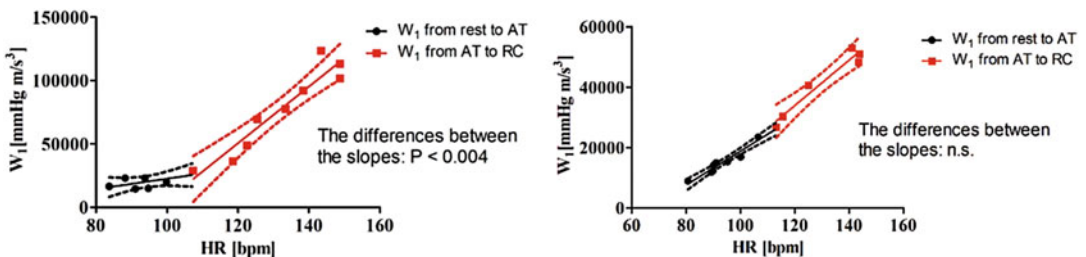


Fig. 11.12 Change in FFR slope during the period from rest to AT and the period from AT to RC in a representative man (left) and a representative woman (right)

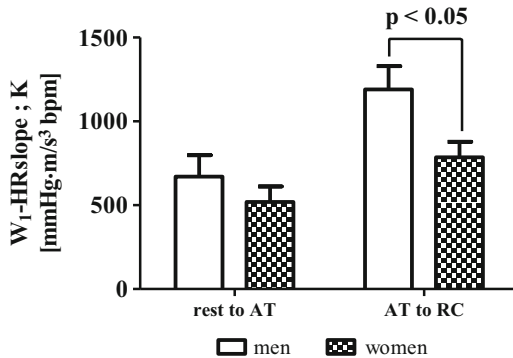


Fig. 11.13 Comparison of FFR (K) slopes during the period from rest to AT and the period from AT to RC between men and women

In this study, P_s/P_d did not differ between men and women during exercise. However, $(D_s - D_d)/D_d$ in men increased during exercise, but it did not change in women. As a result, β did not change in men, but it increased in women during exercise according to Eq. (11.14). This may have caused an impairment of LV-ejection performance as discussed previously. There were no differences in W_1 , the contractility index, between men and women at rest and AT. However, women had lower W_1 at RC. The slope of FFR (W_1 -HR relation) is another manifestation of LV-ejection performance. In men, the slope of FFR suddenly increased at AT, but it did not change significantly up to RC in women. There were no differences in FFR slope between men and women during the period from rest to AT, but FFR slope was greater in men than women during the period from AT to RC.

Conclusions

The reached values of workload/weight at RC, VCO_2 and VO_2 at AT and at RC, W_1 at RC, and the slopes of the FFR during the period from AT to RC were greater in men than women.

The mechanism of these differences is still the target of further investigations.

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